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2019-05

Kauppila , T K , Paassilta , M , Kukkonen , A K , Kuitunen , M , Pelkonen , A S & Makela , M J 2019 , ' Outcome of oral immunotherapy for persistent cow's milk allergy from 11 years of experience in Finland ' , Pediatric Allergy and Immunology , vol. 30 , no. 3 , pp. 356-362 . https://doi.org/10.1111/pai.

http://hdl.handle.net/10138/314614
https://doi.org/10.1111/pai.13025

acceptedVersion

Received: 14 June 2018 | Revised: 20 December 2018 | Accepted: 15 January 2019

DOI: 10.1111/pai.13025

ORIGINAL ARTICLE

WILEY

Outcome of oral immunotherapy for persistent cow's milk allergy from 11 years of experience in Finland

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Funding information
This study has been supported by the Paediatric Research Foundation of Finland, the Finnish Society of Allergology and Immunology, Sigrid Juselius Foundation, State funding for university-level health research, and the Allergy Research Foundation.

Edited by: Alexandra Santos

Abstract

Background: The safety and efficacy of long-term milk oral immunotherapy (OIT) in Finnish children with persistent cow's milk allergy (CMA) were evaluated in an open-label, non-randomized study.

Methods: During the 11-year study, 296 children aged 5 years or older with immunoglobulin E (IgE)-mediated CMA started milk OIT. Follow-up data were collected at three time points: the post-buildup phase, 1 year thereafter, and at the cross-sectional long-term follow-up between January 2016 and December 2017. Patients were divided according to baseline milk-specific IgE (sIgE) level and by the amount of milk consumption at the long-term follow-up. The high-dose group consumed ≥2 dL of milk daily, while the failure group consumed <2 dL of milk or were on a milk-avoidance diet.

Results: Out of the initial study group, 244/296 (83%) patients participated in the long-term follow-up. Among these patients, 136/244 (56%) consumed ≥2 dL of milk daily. The median follow-up time was 6.5 years. Of the recorded markers and clinical factors, the baseline milk sIgE level was most associated with maintaining milk OIT ($P < 0.001$). Respiratory symptoms in the post-buildup phase increased the risk of treatment failure (OR 3.5, 95% CI: 1.5-8.1, $P = 0.003$) and anaphylaxis (OR 14.3, 95% CI: 1.8-114, $P = 0.01$).

Conclusion: More than half of the patients were able to maintain the targeted milk dose in their daily diet. Baseline milk sIgE level and reactivity during the early treatment stage strongly predicted the long-term outcome and safety of milk OIT.

KEYWORDS
children, desensitization, food allergy, IgE, milk allergy, oral immunotherapy, prognosis

1 | INTRODUCTION

Food allergies and their increasing prevalence have been the subject of intensive research in recent decades.[1] Cow's milk allergy (CMA) is one of the most common food allergies. According to Finnish national records and a cohort study in Europe, the incidence of challenge-proven CMA is 0.5% in young children.[2-4] Although most children outgrow their milk allergies, children with severe milk allergies tend to have persistent CMA.[5-7] The recommended treatment for food allergies is allergy avoidance,[1] but milk oral immunotherapy (OIT) has shown promise in promoting desensitization to cow's milk protein in children with persistent CMA.[8-12] Long-term outcomes of milk OIT have been published in small studies, with success rates varying from 31% to 65%.[13-15] More long-term follow-up studies on OIT are needed.[8]

This study was based on previous milk OIT studies conducted in Finland.[12,15-18] By gathering real-life results from previous

clinical studies, we were able to monitor the effects of milk OIT in 296 patients over 11 years. We examined milk consumption over time, OIT safety, the reasons for OIT discontinuation, and the risk factors for treatment failure and anaphylaxis.

2 | METHODS

2.1 | Study design

An open-label, non-randomized milk OIT study started in 2005 at the Skin and Allergy Hospital, Helsinki, Finland (Study Unit 1). Study Unit 2 started milk OIT in 2008 at the Department of Pediatrics, Tampere University Hospital. The two study units followed similar milk OIT protocols adapted from Meglio et al.[9] Briefly, patients aged ≥5 years with IgE-mediated, open milk challenge-positive CMA started milk OIT. Escalating doses of milk protein were administered daily at home, starting from 0.5 μg to the maintenance dose of 6.4 g (approximately 2 dL of milk) during a 4-month buildup phase with daily antihistamine (Table S1).

2.2 | Follow-up and data collection

Data were collected at three time points: (a) the post-buildup phase, which occurred 3 months after reaching the maintenance dose (visit); (b) 1 year thereafter (visit; data not shown) or at the time when the patient discontinued treatment; and (c) a cross-sectional long-term follow-up between January 2016 and December 2017 for all patients (mailed questionnaire or phone call if the patient did not answer the questionnaire). Data were assembled from both the questionnaires and patient records. The patients were divided into three groups according to their long-term milk consumption. The high-dose group consumed ≥2 dL of milk per day (or equal amount of milk protein), while the failure group combined the low-dose group (consumed <2 dL of milk or equal amount of milk protein) and the avoidance group (milk-free diet). Anaphylaxes, as defined by the World Allergy Organization,[19] were determined from the questionnaires (both study units) and patient records (Study Unit 1).

2.3 | Ethics

The Institutional Ethics Committees of the Helsinki University Hospitals and the University Hospitals of Helsinki and Tampere approved the study protocol and the follow-up study. The follow-up study was registered at ClinicalTrials.gov (number NCT02640014).

2.4 | Statistical analyses

Distributional differences in the clinical variables were compared with Fisher's chi-square test and nonparametric Mann-Whitney *U* test or Kruskal-Wallis test. Kaplan-Meier analysis was performed to measure the relationships between the participants who maintained milk OIT and their baseline milk-specific IgE (sIgE) level with a log-rank test. The time to first discontinuation or the end of follow-up was measured as the years since the patient began milk OIT as a time metric. Logistic regression analyses were used to define risk factors for OIT outcomes. Log_2 transformation was assessed for sIgE level when needed. The reported *P* values are two-tailed, when applicable, and values <0.05 were considered statistically significant. The SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY, USA) and the Prism 6 software (GraphPad, San Diego, CA, USA) were used for the analyses.

3 | RESULTS

3.1 | Milk consumption

During the 11-year study period, 296 patients began milk OIT (202 patients in Study Unit 1 and 94 patients in Study Unit 2; Figure 1, Figure S1). Long-term follow-up data on milk consumption were available for 244/296 (83%) patients. Among these patients, 136/244 (56%) consumed ≥2 dL of milk daily, 44/244 (18%) consumed <2 dL,

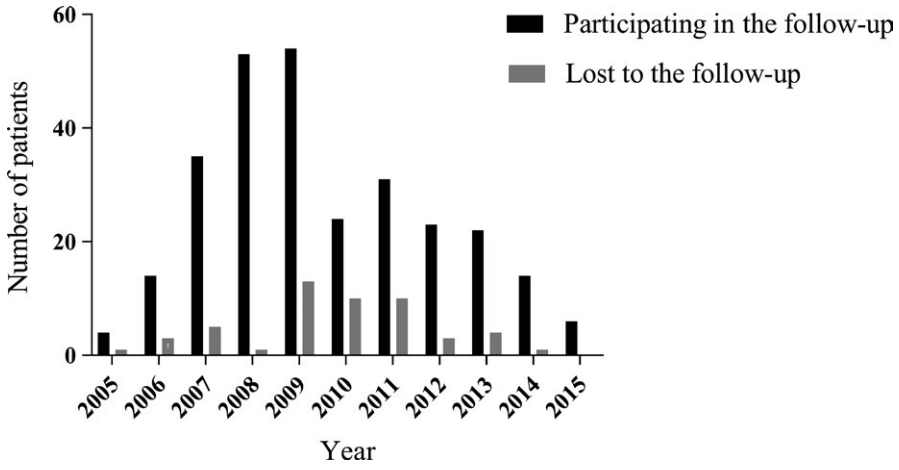

FIGURE 1 The number of patients starting milk OIT each year divided by the number of patients participating through the follow-up

TABLE 1 A summary of the patients' characteristics in the baseline, post-buildup phase, and long term, grouped by their long-term milk consumption

Characteristic	High-dose group (n = 136)	Low-dose group (n = 44)	Avoidance group (n = 64)	*P* value
Baseline				
Male sex	79 (58)	26 (59)	36 (56)	0.95
Age (years) when OIT was started	7.5 (5-17)	7.0 (5-14)	8.0 (5-16)	0.24
Asthma	100 (74)	29/44 (66)	49/64 (77)	0.32
Atopic skin	86 (63)	36/44 (88)	42/63 (67)	0.12
Baseline milk IgE (kU_A/L), data missing from 1	12 (0.3-9200)	26 (0.8-942)	77 (2-2450)	**0.000**
Baseline OFC cumulative threshold, milk protein dose (mg)[a]	396 (0-5379)	99 (0-2079)	10 (4-20)	0.07
Adrenalin used at the baseline milk challenge	6 (4.4)	4 (9)	12 (19)	**0.004**
Post-buildup phase results				
Able to reach the high-dose milk consumption (2 dL)	124 (91)	29 (66)	16/63 (25)	**0.000**
Presence of any milk-related side effects[b]	52/88 (59)	31/35 (89)	39/41 (95)	**0.000**
Treated with adrenalin[b]	1/88 (1.1)	1/36 (2.8)	2/42 (4.8)	0.45
Oral/ocular symptoms[b]	37/66 (56)	18/26 (69)	10/14 (71)	0.20
Cutaneous symptoms[b]	27/66 (41)	11/26 (42)	8/14 (57)	0.53
Respiratory symptoms[b]	26/65 (40)	18/26 (69)	10/14 (71)	**0.01**
GI symptoms[b]	30/66 (45)	19/26 (73)	11/14 (79)	**0.01**
Long-term follow-up results				
Age (years)	14 (7-25)	13 (8-21)	14 (7-24)	0.33
Long-term follow-up time (years)	6.5 (1-11)	6.3 (1-11)	6.4 (1-11)	0.55
Current asthma	81/129 (63)	31/44 (70)	41/58 (71)	0.46
Cur. allergic rhinitis	91/127 (72)	30/43 (70)	40/56 (71)	0.97
Cur. atopic dermatitis	94/127 (74)	34/42 (81)	46/57 (81)	0.48
Average daily milk dose (median dL)	2.0 (2.0-10.0)	1.0 (0.1-1.5)	0.0 (0.0-0.0)	**0.000**
Consuming only baked milk	1 (0.7)	3 (6.8)	0 (0)	**0.01**
Any milk-related side effects in the past year	45/122 (37)	29/36 (81)	30/45 (67)	**0.000**
Treated with adrenalin	2/122 (1.6)	2/36 (5.6)	4/45 (8.9)	0.09
Oral symptoms	28/122 (23)	24/36 (67)	21/45 (47)	**0.000**
Cutaneous symptoms	21/122 (17)	17/36 (47)	17/45 (38)	**0.000**
Respiratory symptoms	20/122 (16)	21/36 (50)	17/45 (38)	**0.000**
GI symptoms	23/122 (19)	18/36 (58)	17/45 (38)	**0.000**
Anaphylaxis at least once after buildup (milk-related)	9/131 (6.9)	6/43 (14)	19/60 (32)	**0.000**

Bold text represents statistical significance ($P < 0.05$).
High-dose group, daily milk consumption ≥2 dL; low-dose group, 0.1-1.9 dL milk in the daily diet; and avoidance group, milk-avoidance diet. sIgE, specific immunoglobulin E; OFC, open food challenge; GI, gastrointestinal. Details for side effects are presented in Table 2.
Values are expressed as n (%) or median (range; min-max).
[a]Data available from Study Unit 1, n = 174
[b]Data available from Study Unit 1.

and 64/244 (26%) were on a milk-avoidance diet. Table 1 presents a summary of the patients' characteristics, grouped by their long-term milk consumption.

Significant differences ($P < 0.001$) in the rates of milk OIT continuance were noted when subjects with different baseline milk sIgE levels were compared (Figure 2). Logistic regression analysis

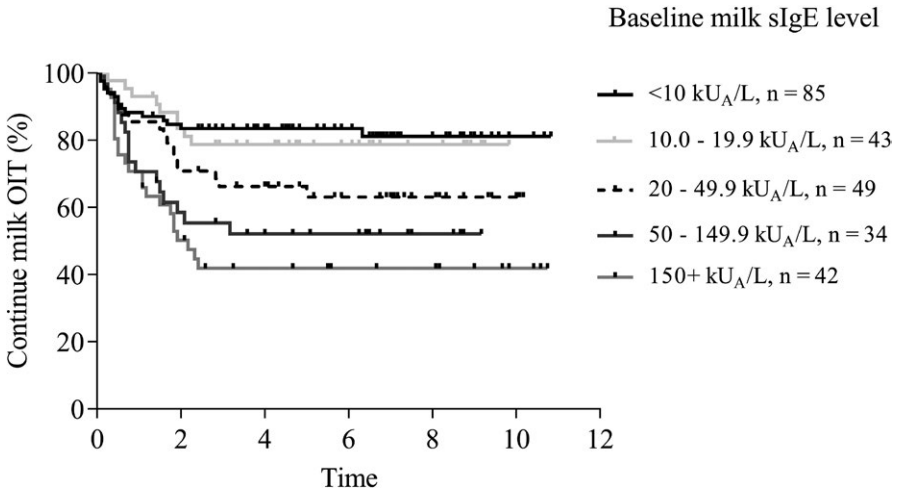

FIGURE 2 Kaplan-Meier analysis representing the relationship between milk OIT continuation and baseline milk sIgE levels, n = 253. A log-rank test was run to determine whether there were differences in the milk OIT continuation distribution for the different levels of baseline milk-specific IgE, *P* = <0.001 (82%, 79%, 63%, 53%, 43%). Time (years)

was conducted to define the effects of the baseline variables and the treatment-related factors on milk OIT failure (Table 2). Other variables, such as gender, the age when OIT was started (<7 years vs older), baseline asthma, rhinitis, atopic disease, and the mother's atopic diseases, were examined, and none were statistically significant predictors of treatment failure (data not shown). The self-reported, milk-related respiratory symptoms in the post-buildup phase were statistically significantly associated with higher median baseline milk sIgE level compared to the patients with no respiratory symptoms (22.6 kU$_A$/L [min 0.21 kU$_A$/L-max 9200 kU$_A$/L] vs 8.9 kU$_A$/L [min 0.26 kU$_A$/L-max 942 kU$_A$/L], *P* = 0.02, Mann-Whitney *U* test). However, self-reported, milk-related gastrointestinal (GI) symptoms in the post-buildup phase were not statistically significantly associated with median baseline milk sIgE level compared to the patients with no GI symptoms (11.7 kU$_A$/L [min 0.21 kU$_A$/L-max 9200 kU$_A$/L] vs 10.6 kU$_A$/L [min 0.26 kU$_A$/L-max 9200 kU$_A$/L] vs 10.6 kU$_A$/L [min 0.26 kU$_A$/L-max 942 kU$_A$/L], *P* = 0.47).

3.2 | Safety

Side effect prevalence is presented in Table 1. Of the patients who participated in the follow-up, 77/244 (32%) consumed ≥2 dL of milk daily with no self-reported, milk-related side effects in the previous year. The patients with longer follow-up time tended to have less side effects, but the difference did not reach statistical difference (*P* = 0.07; Table S2). Anaphylaxes after the buildup phase were reported in 34/237 (14%) patients; data were missing from 59 patients. There was a significant difference in the baseline milk sIgE levels between the patients who experienced anaphylaxis compared to the patients with no reported anaphylaxis after the buildup phase (median 184 kU$_A$/L [min 2.3-max 1870 kU$_A$/L] vs 14 kU$_A$/L [min 0.3-max 9200 kU$_A$/L], *P* = 0.000, Mann-Whitney *U* test). Logistic regression analyses were conducted to further define the risk factors for anaphylaxis (Table 2).

Eight patients reported using intramuscular adrenalin during the previous year in the long-term follow-up questionnaire. Two of the eight had been consuming ≥2 dL of milk for over 9 years. Both had asthma and high baseline milk sIgE levels (>250 kU$_A$/L). One of the anaphylaxes was related to unlimited milk consumption with exercise, and the other occurred after accidental exposure to an unfamiliar milk product. There was one unexpected reaction related to the reduced daily milk dose (<2 dL) after 4 years of treatment, and one reaction in a patient who was still in the buildup phase at the time of the reaction. Four patients had an accidental reaction to milk while on avoidance diets and used adrenalin. One extremely severe anaphylaxis happened during the study. This reaction occurred after consumption of milk yogurt with a high concentration of cow's milk protein (8 g/100 mL), while he was on the aimed maintenance dose. This boy suffered from moderate-to-severe asthma and was experiencing an exacerbation of that condition at the time of the anaphylaxis. He had a high baseline milk sIgE level (>500 kU$_A$/L). The subject required resuscitation and intubation but recovered fully without sequelae; his milk OIT was discontinued.

3.3 | OIT discontinuation

A total of 71/252 (28%) patients discontinued milk OIT during the study period; the data were missing from 44/296 (15%) patients. Most patients (48/71, 68%) reported multiple reasons for discontinuation, with the most common self-reported reason being GI symptoms (41/71, 58%). Reported GI symptoms included abdominal pain (16/41, 39%), nausea (15/41, 37%), vomiting (11/41, 27%), dysphagia (8/41, 20%), and bloody stools (1/41, 2%). One patient with vomiting and failure to thrive had an endoscopy to check for possible eosinophilic esophagitis (EoE). The endoscopy results were negative for EoE, but the examination was performed after OIT discontinuation and while the patient was on a milk-avoidance diet. Other reasons for OIT discontinuation included cutaneous symptoms (34/71, 48%), respiratory symptoms (24/71, 34%), anaphylaxis (22/71, 31%),

TABLE 2 Logistic regression analysis (using a log2-transformed IgE concentration) of the milk OIT-related variables and their relation to the milk OIT outcomes (analysis with one variable in the model at a time)

Outcome	Variable	Odds ratio	95% CI	*P* value
Treatment failure	Milk sIgE before OIT[a]	1.3	1.2-1.5	**0.000**
	Adrenalin used at the baseline milk challenge	3.8	1.4-10	**0.008**
	Oral symptoms in the post-buildup phase[b]	2.1	0.9-4.8	0.09
	Cutaneous symptoms in the post-buildup phase[b]	1.3	0.6-2.9	0.51
	GI symptoms in the post-buildup phase[b]	3.6	1.5-8.5	**0.004**
	Respiratory tract symptoms in the post-buildup phase[b]	3.5	1.5-8.1	**0.003**
	Milk-related anaphylaxis after buildup	4.4	1.9-9.8	**0.000**
Milk-related anaphylaxis after buildup	Milk sIgE before OIT	1.6	1.3-1.8	**0.000**
	Adrenalin used at the baseline milk challenge	2.0	0.7-5.9	0.21
	Oral symptoms in the post-buildup phase[b]	4.0	0.8-19	0.08
	Cutaneous symptoms in the post-buildup phase[b]	3.4	0.98-12	0.054
	GI symptoms in the post-buildup phase[b]	5.2	1.1-25	**0.04**
	Respiratory tract symptoms in the post-buildup phase[b]	14.3	1.8-114	**0.01**

Bold text represents statistical significance ($P < .05$).

OIT, oral immunotherapy; sIgE, specific immunoglobulin E; GI, gastrointestinal. Treatment failure—not able to maintain long-term ≤2 dL milk dose.

[a]1.30 is the odds ratio for the baseline milk-specific IgE level, indicating that for every additional doubling of the specific IgE level, the risk of OIT failure increases by 1.30 times or by 30%.

[b]The presence of any type (self-reported) of oral symptoms (eg, itching, dryness/discomfort, swelling of the oral cavity, lips, tongue, and/or pharynx) or cutaneous symptoms (acute or delayed, eg, pruritus, erythema/flushing, urticaria, angioedema, contact urticaria) or GI (eg, abdominal pain, nausea, emesis, vomiting, or dysphagia) or respiratory tract symptoms (eg, nasal congestion, rhinorrhea, sneezing, hoarseness, laryngeal edema, dysphonia, shortness of breath, cough, or wheezing)[27] related to milk consumption, data available from Study Unit 1, n = 105.

oropharyngeal side effects (21/71, 30%), disliking the taste of milk (7/71, 10%), ocular symptoms (5/71, 7%), no progress in the treatment (4/71, 6%), and miscellaneous symptoms (failure to thrive, trouble sleeping, taking milk was more demanding than avoidance, or behavioral changes such as tearfulness) (8/71, 11%). Median time since the beginning of the OIT to the discontinuation was 9 months (min 0-max 76 months).

3.4 | Lost to follow-up

Overall, 51/296 (17%) patients were lost by the time of the long-term follow-up (Figure S1). There was no statistical difference between the gender of the lost patients and those who participated in the long-term follow-up. The lost patients were older at the start of their milk OIT (median age 9 years vs 7 years, $P = 0.038$, Mann-Whitney *U* test), and they had lower baseline milk sIgE levels compared to the patients who participated in the long-term follow-up (median 8.5 kU_A/L vs 18 kU_A/L, $P = 0.044$, Mann-Whitney *U* test).

4 | DISCUSSION

This report describes the results from 11 years of milk OIT in a clinical study based on real-life experiences. More than half (56%) of the study participants maintained a high daily dose of milk consumption. However, some severe reactions occurred. Higher baseline milk sIgE level and early treatment reactivity strongly predicted the risk of treatment failure and anaphylaxis.

Previously published long-term milk OIT studies have had small sample sizes, and the follow-up time has varied from 4.5 to 7 years.[13-15] This study included a large sample size (n = 296) with a median follow-up of 6.5 years. We did not exclude children with high milk sIgE level or asthma. When necessary, a patient's asthma status was controlled before starting milk OIT. In a previous milk OIT study, asthma was related to a worse long-term outcome.[20] Similarly, in our study, the presence of any type of milk-related respiratory symptom in the post-buildup phase increased the risk of treatment failure. Respiratory symptoms were associated with higher baseline milk sIgE level. Higher baseline tolerated milk amounts and not requiring adrenalin at the baseline food challenge have been identified as short-term predictors for achieving a full milk dose.[21] Our study reinforced these findings and extended these factors to long-term predictors of maintaining a high milk dose.

The relationship between baseline milk sIgE level and milk OIT outcome has been previously published.[14,15,18,22] This phenomenon has also been seen in the prevalence of children who outgrow their milk allergy[5-7] and in food challenges.[23] A lower milk sIgE level is related to a better outcome. This study provides practical information for evaluating the risk of treatment discontinuation. Using this study, a patient with a certain baseline milk sIgE level can evaluate the likelihood of continuing treatment. When the baseline milk sIgE level was <10 kU_A/L, 82% of the patients were able to consume milk, compared to baseline milk sIgE level over 150 kU_A/L, where 43% of the patients were able to consume milk over time. However, care should be taken when applying the data presented in Figure 2, as

the numbers do not differentiate the amount of milk that the patient consumed.

The increased risk of EoE related to OIT has been highlighted in the literature. The rate of biopsy-confirmed EoE in the analysis of multiple milk OIT studies was 5.4%.[24] Notably, GI symptoms were the most commonly cited reason for patients discontinuing milk OIT. There are similarities between EoE symptoms and the symptoms that our patients reported (ie, failure to thrive, nausea, vomiting, abdominal pain, and dysphagia).[24] An endoscopy was performed on one patient in the study group. The result of that endoscopy was negative for EoE, but the examination was performed when the patient was on a milk-avoidance diet. Our study revealed some intriguing GI-related associations. There was a strong correlation between self-reported, milk-related GI symptoms in the post-buildup phase and treatment failure ($P = 0.004$), but unlike respiratory symptoms, GI symptoms in the post-buildup phase were not associated with baseline milk sIgE level ($P = 0.47$). Parenthetically, the development of EoE is not driven by IgE.[1]

The reasons cited for milk OIT discontinuation in our study and the severe reactions related to milk OIT seen in our patients have both been described in the literature.[25,26] One extremely severe reaction occurred during the study, and two patients reported having to use adrenalin after 9 years of daily milk consumption. These severe reactions were related to OIT protocol deviations (ie, consumption of a high-milk protein product, unlimited milk consumption, and consumption of an unfamiliar milk product), and the affected patients had high baseline milk sIgE level and asthma. The EAACI guidelines highlight the crucial role of protocol adherence to ensure both safety and efficacy.[27]

There are limitations to our study. First, there was no control group, so the study cannot answer the question of how many of the studied children would have grown out of their allergies naturally without milk OIT. While it is highly possible that some patients might have improved on their own (especially the ones with low baseline milk sIgE level who tolerated larger amounts of milk protein in the baseline OFC), our patients were above the age when milk allergies tend to resolve naturally,[5] and CMA diagnosis was confirmed before the patients started OIT. It is also possible that some of our patients with low baseline milk sIgE level would have been able to introduce baked milk to their diet. Second, we did not study sustained unresponsiveness by performing treatment discontinuation and rechallenges. Likewise, milk consumption at the long-term follow-up was based on self-reported questionnaire data.

The third limitation of our study was that 17% of the patients were lost during the long-term follow-up. The patients who were missing at the follow-up had lower baseline milk sIgE level indicating that their milk allergy might have been less severe. This discrepancy might have affected our results, as a larger portion of the study patients might be consuming milk over the long term than is reflected in our data. However, the study by Keet et al[14] reported that 22% (7/32) of patients were consuming milk with no symptoms over the long term, while in our study, 32% of the patients were consuming ≥2 dL of milk daily with no symptoms in the previous year. In addition, there were gaps in the follow-up data due to the practicalities of collecting real-life evidence. We also observed some unexpected changes in milk consumption over time (eg, 12 patients increased their milk consumption after the post-buildup phase).

The strengths of our study include the large sample size, the follow-up data collected over the course of up to 11 years, and the analysis of milk OIT in a real-life setting. While long-term safety has not been fully assessed in this field,[27] this study provides practical knowledge on the long-term use of milk OIT and highlights factors that might identify high-risk patients. In this study, patients consuming low daily doses of milk were placed in the treatment failure group along with patients who had discontinued milk OIT. However, the low-dose group might still have benefitted from their milk consumption, as their self-reported median milk dose was 32 times higher than their milk threshold level at the baseline milk challenge (Table 1).

In summary, this study suggests that OIT for the treatment of persistent milk allergy is most efficacious in patients with low baseline milk sIgE level. Baseline characteristics and early treatment reactivity strongly predicted the risk of later treatment failure and anaphylaxis. More than half of the patients were able to maintain a high daily dose of milk, and nearly three-fourths of the patients continued at least some level of milk consumption.

ACKNOWLEDGMENTS

We are collectively grateful to all the pediatricians and nurses who participated in the patient recruitment at the two study units. We thank the milk-allergic children and their families for participation in this clinical trial. We would like to thank Stephanie Leonard, MD for consultation regarding the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Renz H, Allen K, Sicherer S, et al. Food allergy. *Nat Rev Dis Primers*. 2018;4:17098.
2. Official Statistics of Finland: Population structure [e-publication]. The amount of under 5 years old in 2016 was 287 537. Helsinki: Statistics Finland. http://www.stat.fi/til/vaerak/index_en.html. Accessed Jan 3, 2018.
3. Official Statistics of Finland: Statistic of sickness allowance [e-publication]. The amount of children under 5 years of age to receive disability allowance because of a challenge proven milk allergy was 1441 in 2016. Helsinki: Kela. http://www.kela.fi/tilastot-aiheittain_tilasto-sairaanhoitokorvauksista. Accessed Jan 3, 2018.

4. Schoemaker AA, Sprikkelman AB, Grimshaw KE, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children-EuroPrevall birth cohort. *Allergy*. 2015;70:963-972.
5. Saarinen KM, Pelkonen AS, Mäkelä MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol*. 2005;116:869-875.
6. Wood R, Sicherer S, Vickery B, et al. The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol*. 2013;131:805-812.
7. Skripak J, Matsui E, Mudd K, Wood R. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol*. 2007;120:1172-1177.
8. Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy*. 2017;72:1133-1147.
9. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy*. 2004;59:980-987.
10. Skripak JM, Nash SD, Rowley H, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol*. 2008;122:1154-1160.
11. Longo G, Barbi E, Berti I, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol*. 2008;121:343-347.
12. Salmivesi S, Korppi M, Mäkelä MJ, Paassilta M. Milk oral immunotherapy is effective in school-aged children. *Acta Paediatr*. 2013;102:172-176.
13. Meglio P, Giampietro PG, Gianni S, Galli E. Oral desensitization in children with immunoglobulin E-mediated cow's milk allergy-follow-up at 4 yr and 8 months. *Pediatr Allergy Immunol*. 2008;19:412-419.
14. Keet CA, Seopaul S, Knorr S, Narisety S, Skripak J, Wood RA. Long-term follow-up of oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol*. 2013;132:737-739.
15. Paassilta M, Salmivesi S, Mäki T, Helminen M, Korppi M. Children who were treated with oral immunotherapy for cows' milk allergy showed long-term desensitization seven years later. *Acta Paediatr*. 2016;105:215-219.
16. Savilahti EM, Kuitunen M, Savilahti E, Mäkelä MJ. Specific antibodies in oral immunotherapy for cow's milk allergy: kinetics and prediction of clinical outcome. *Int Arch Allergy Immunol*. 2014;164:32-39.
17. Savilahti EM, Kuitunen M, Valori M, et al. Use of IgE and IgG4 epitope binding to predict the outcome of oral immunotherapy in cow's milk allergy. *Pediatr Allergy Immunol*. 2014;25:227-235.
18. Kuitunen M, Englund H, Remes S, et al. High IgE levels to α-lactalbumin, β-lactoglobulin and casein predict less successful cow's milk oral immunotherapy. *Allergy*. 2015;70:955-962.
19. Simons FE, Ardusso LR, Dimov V, et al. World Allergy Organization anaphylaxis guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol*. 2013;162:193-204.
20. Elizur A, Goldberg M, Levy M, Nachson L, Katz Y. Oral immunotherapy in cow´s milk allergic patients: course and long-term outcome according to asthma status. *Ann Allergy Asthma Immunol*. 2015;114:240-244.
21. Levy MB, Elizur A, Goldberg MR, Nachshon L, Katz Y. Clinical predictors for favorable outcomes in an oral immunotherapy program for IgE-mediated cow's milk allergy. *Ann Allergy Asthma Immunol*. 2014;112:58-63.
22. Vázquez-Ortiz M, Álvaro-Lozano M, Alsina L, et al. Safety and predictors of adverse events during oral immunotherapy for milk allergy: severity of reaction at oral challenge, specific IgE and prick test. *Clin Exp Allergy*. 2013;43:92-102.
23. Ynagida N, Sato S, Takahashi K, et al. Increasing specific immunoglobulin E levels correlate with the risk of anaphylaxis during an oral food challenge. *Pediatr Allergy Immunol*. 2018;29(4):417-424.
24. Petroni P, Spergel J. Eosinophilic esophagitis and symptoms possibly related to eosinophilic esophagitis in oral immunotherapy. *Ann Allergy Asthma Immunol*. 2018;120:237-240.
25. Mori F, Cianferoni A, Brambilla A, et al. Side effects and their impact on the success of milk oral immunotherapy (OIT) in children. *Int J Immunopathol Pharmacol*. 2017;30:182-187.
26. Vazquez-Ortiz M, Alvaro M, Piquer M, et al. Life-threatening anaphylaxis to egg and milk oral immunotherapy in asthmatic teenagers. *Ann Allergy Asthma Immunol*. 2014;113:482-484.
27. Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy*. 2018;73:799-815.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Kauppila TK, Paassilta M, Kukkonen AK, Kuitunen M, Pelkonen AS, Makela MJ. Outcome of oral immunotherapy for persistent cow's milk allergy from 11 years of experience in Finland. *Pediatr Allergy Immunol*. 2019;00:1–7. https://doi.org/10.1111/pai.13025